HEMATOLOGICAL PROFILE OF PEOPLE LIVING WITH HIV / AIDS

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BRANCH - I DEGREE EXAMINATION

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CERTIFICATE

This is to certify that the dissertation entitled "***Hematological profile of people living with HIV/AIDS***" presented here is the original work done by Dr.R.ASHOK KUMAR, postgraduate at the Institute of Internal Medicine, Madras Medical College, Govt. General Hospital, Chennai-600 003 in partial fulfillment of the University rules and regulations for the award of M.D. Degree Branch - I (General Medicine) under my guidance and supervision during the academic period from 2005-2008.

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DECLARATION

I solemnly declare that this dissertation entitled "***Hematological profile of people living with HIV/AIDS***" was done by me at Madras Medical College and Govt. General Hospital during 2005-2008 under the guidance and supervision of Prof. M. Jubilee, M.D., This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree Branch I (General Medicine).

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CONTENTS

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Ref. No.: 12299 / P&D / Ethics / Dean / GGH / Chennai, dated July 19th, 2007

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The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on **July 19th 2007**, at the conference hall of the Dean, Tower Block I, GGH, Chennai.

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HEMATOLOGICAL PROFILE OF PEOPLE LIVING WITH HIV/AIDS (PLHA'S)

INTRODUCTION:

The HIV epidemic, is a convincing illustration of the balance between the power of science and the humanism of modern medicine. The epidemic is so serious that between 1981 and 2000, 21.8 million people had died of HIV/AIDS[1].

Clinically significant hematologic abnormalities are common in HIV infection. Hematologic abnormalities are among the most common complications of infection with HIV[2]. These abnormalities are due to:

- Impaired hematopoiesis
- Immune mediated cytopenias and
- Altered coagulation mechanisms

These abnormalities may occur as a result of HIV infection itself, as sequelae of HIV related opportunistic infections or malignancies or as a consequence of therapies used for HIV infection and associated conditions.

Despite the availability of various categories of diagnostic and monitoring techniques for HIV/AIDs, the costs of it are still unaffordable to several people in the resource poor settings. Early identification of the hematologic abnormalities would lead to appropriate planning of treatment strategies.

Hence, this study was conducted in order to know the pattern of these hematologic abnormalities among PLHA’s.

AIMS AND OBJECTIVES

1. To analyse the hematological profile of people living with HIV/AIDS (PLHA's)

2. To identify the possible correlation between WHO clinical stage and hematological abnormalities if any.

REVIEW OF LITERATURE

Disorders of the hematopoietic system including lymphadenopathy, anemia, leucopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy. Direct histologic examination and culture of lymph node or bone marrow tissue are often diagnostic. A significant percentage of bone marrow aspirates from patients with HIV infection have been reported to contain lymphoid aggregates, the precise significance of which is unknown. Initiation of HAART will lead to reversal of most hematologic complications that are the direct result of HIV infection.

Hematologic abnormalities secondary to HIV infection include anemia, neutropenia, thrombocytopenia, venous thrombo embolism, hemophagocytic syndrome, AIDS - related lymphoma including primary effusion lymphoma, castlemann’s disease and rarely Hodgkin’s disease and myeloma.

ANEMIA:

Anemia is common in HIV-infected individuals occuring in approximately 10 to 20% at initial presentation and diagnosed in approximately 70 to 80% of patients over the course of disease[3,5]. The incidence increases with the clinical stage of disease. It is dependent of CD4 count and viral load i.e. frequency and severity of anemia appear to correlate with HIV related factors such as

i) CD4 counts less than 200 cells/microlitre.

ii) Higher plasma HIV-1 RNA levels, and

iii) History of clinical AIDS defining condition[6,7]

On the contrary presence of anemia in HIV infected patient is significantly associated with an increased risk of death, and this is independent of the CD4 count and viral load[8,9].

In a study among patients receiving no myelosuppressive therapies 8% of asymptomatic HIV seropositive patients, 20% of those with symptomatic HIV disease, 91% of those with centre for disease control (CDC) defined AIDS were anemic[10]. The viral activated transfusion study[11,12] found that the frequency of

transfusion for anemia decreased after institution of HAART when compared to historical controls[5].

CAUSES OF ANEMIA:

I) Decreased production of red blood cells

II) Increased red cell destruction

III) Ineffective production of red cells

I) Decreased production of red blood cells:

A decrease in red blood cell (RBC) production may result from factors:

i) suppression of the CD 34+ colony forming unit - granulocyte - erythroid - monocyte - macrophage by inflammatory cytokines or the HIV virus itself[3,4].

ii) Blunted production of erythropoietin - documented in anemic HIV-infected patients, similar to the suppression observed in other states of chronic infection or inflammation[12].

iii) Infiltration of the marrow by tumour such as lymphoma[13] or infection such as mycobacterium avium complex (MAC). All these may lead to decreased production of RBC's.

In addition, MAC may also be associated with cytokines - induced marrow suppression. Involvement of GI tract by various infections (or) tumours may lead to chronic blood loss, with eventual iron deficiency anemia.

Another important cause of hypoproliferative anemia in patients with HIV infection is medications particularly ART drug zidovudine (AZT). AZT, the first licensed anti retroviral agent is uniformly associated with macrocytosis (Mean cell volume >100fl), which can be used as an objective indication that the patient has been compliant with this medication[14].

Transfusion dependent anemia (Hb <8.5g/dl) has been reported in approximately 30% of patients with full blown AIDS who were receiving AZT at doses of 600mg/day. Incidence of severe anemia is only 1% when the same dose of AZT is used in patients with asymptomatic HIV disease[15].

Infection of the marrow by Parvo virus B19 is another cause of hypoproliferative anemia in HIV-infected patients, resulting in specific infection of the pronormoblast[16,17]. Although marrow failure affecting all three cell lines has been described with parvovirus B19 infection, a pure red cell aplasia is the usual consequence.

Approximately 85% of adults have serologic evidence of prior parvo virus infection, but among HIV infected patients it is only 64%. The diagnosis of parvovirus B19 can be made on marrow examination, revealing giant pronormoblasts with clumped basophilic chromatin and clear cytoplasmic vacuoles.

Diagnosis can be confirmed by in situ hybidization using sequence-specific DNA probes. Therapy for parovirus induced red cell aplasia consists of infusion of intervenous γ-globulin (IVIG) from plasma donors.

ii) Increased red cell destruction:

Increased red cell destruction may be seen in HIV infected patients with Glucose 6 phosphate dehydrogenase (G-6PD) deficiency who are exposed to oxidant drugs and in patients with

disseminated intravascular coagulation (DIC) or thrombotic throbocytopenic purpura[18].

Presence of fragmented RBC's and thrombocytopenia is seen in the latter two conditions and Heinz bodies in G-6PD deficiency. Hemophagocytic syndrome has been described in HIV infection[19,20]. The development of autoantibodies, with resultant positive coombs test and shortened red cell survival is an additional cause of red cell destruction.

Direct coomb positive test has been reported in 18 to 77% of HIV infected patients although actual hemolysis is low[21]. When present, anti-I antibody and anti body against auto-u antigens have been described in 64% and 32% of patients respectively[22,23].

A high incidence of positive direct coombs test results has been detected in patients with other hypergamma globulinemic states indicating that it may be secondary to the polyclonal hypergamma globulinemia known to occur in HIV infection[24].

iii) Ineffective production of red cells:

Folic acid is absorbed in the jejunum and is responsible for one carbon transfer reactions. Deficiency leads to megaloblastic

anemia and decrease in all three cell lines. HIV infected patients who are ill and not eating properly and those with underlying disease of the jejunum may be unable to absorb sufficient folic acid.

Absorption of vitamin B_{12} requires production of intrinsic factor by parietal cells in the stomach with subsequent absorption in ileum. Vitamin B_{12} malabsorption occurs in HIV infection because of myriad of infections and other disorders of small intestine. Negative B_{12} balance has been documented in approximately one third of patients with AIDS, the majority being defective absorption[25].

Sub acute combined degeneration of the cord occurs in B_{12} deficiency and should be considered in HIV infected patients with neurologic symptoms.

CONSEQUENCES OF ANEMIA IN HIV INFECTION:

i) Decreased Survival

ii) Disease Progression

iii) Impaired quality of life

i) Decreased Survival:

Several large cohort studies have shown that anemia is an independent risk factor for shorter survival in HIV infected patients[6,26].

In the multi state adult and adolescent spectrum of HIV disease surveillance project, anemia was found to be associated with an increased risk of death for all CD4 ranges[5]. Risk of death was increased by 60% for anemic patients with CD4 count <200 cells/microlitre.

Recovery from anemia was shown to be independently associated with improved survival. A study of 6725 European HIV infected patients showed independent prognostic factors for Survivals as:

i) Hb at base line

ii) CD4 count and

iii) Viral load

For each 1g/dl decrease in Hb level, the relative hazard of death was 1.39 (9.5% confidence interval 1.34-1.43)

ii) Disease Progression:

Anemia has been shown to be independently associated with rapid clinical progression of HIV infection. In a cohort study factors related to disease progression were found as:

i) most recent Hb level

ii) CD4 count

iii) HIV 1 viral load and

iv) a history of clinical AIDS before initiation of HAART. With mild anemia the relative hazard of disease progression or death was 2.2 (95% CI 1.6 - 2.9) whereas for severe anemia it was 7.1 (95% CI 2.5 -20.1).

iii) Quality of life parameters:

Anemia has been associated with decrease in quality of life (QOL) as measured by the linear Analogue self assessment (LASA) scale and other such instruments[28,29].

NEUTROPENIA

ETIOLOGY:

Neutropenia is reported in approximately 10% of patients with early asymptomatic HIV infection and in more than 50% of individuals with more advanced HIV-related immunodeficiency[3,4,30]. Decreased colony growth of the progenitor cell colony forming unit - granulocyte - Macrophage[31] may lead to decreased growth of both granulocytes and monocytes.

Soluble inhibitory substances produced by HIV-infected cells have been noted to suppress neutrophils production in vitro. suggesting that autoimmunity plays a part in the development of neutropenia in HIV infection[32].

However studies have shown that the presence of neutrophil bound Ig correlates best with stage of disease rather than neutropenia per se[33].

Decreased serum levels of granulocyte colony stimulating factor (G-CSF) have been described in HIV seropositive subjects with afebrile neutropenia (<1000/microlitre) suggesting that a

relative deficiency of this growth factor may contribute to persistent neutropenia[34].

The other causes of neutropenia in HIV infection includes

i) presence of opportunistic infections.

ii) malignancies and

iii) HIV related myelodysplasia affecting marrow function[35].

Myelosuppression and neutropenia may also result from any of the medications used. HIV infection also causes decreased function of granulocytes and monocytes. Abnormal FC processing by macrophages has been described.

Decreased opsonization and intra cellular killing of bacterial or fungal organisms by granulocytes have been noted[36].

CONSEQUENCES OF NEUTROPENIA:

Multiple studies have shown that the risk of bacterial infection rises when the absolute neutrophil count (ANC) falls below 1000/microlitre and increases further when the ANC falls below 500/mircolitre[37].

Moore and colleagues[38] found that the risk of bacterial infection increases to 2.3 fold and 7.9 fold in HIV infected individuals with ANC less than 1000/ml and 500/ml respectively.

On multivariate analysis the severity and duration of neutropenia were found to be significant predictors of the incidence of hospitalization for serious bacterial infection[39].

On multivariate analysis the three factors independently associated with infectious complications were

i) Presence of a central venous catheter

ii) Neutropenia in the past 3 months and

(i) A lower nadir of granulocyte count.

Among patients with medication associated neutropenia, the most common cause was AZT, followed by cotrimoxazole and ganciclovir. Neutropenia was less likely to be associated with infection in these patients than in individuals on cancer chemotherapy[40].

LYMPHOPENIA

The immune system of patients with HIV infection are characterized by a profound increase in lymphocyte turnover that is immediately reduced with effective and retroviral therapy. Studies utilizing in vivo or in vitro labelling of lymphocytes in the S-phase of the cell cycle have demonstrated a tight correlation between the degree of lymphocyte turnover and plasma levels of HIV RNA. This increase in turnover is seen in CD4+ and CD8+ T lymphocytes as well as B lymphocytes and can be observed in peripheral blood and lymphoid tissue. Mathematical models derived from these data suggest that one can view the lymphoid pool as consisting of dynamically distinct subpopulations of cells that are differentially affected by HIV infection. A major consequence of HIV infection appears to be a shift in cells from a more quiescent pool to a pool with a higher turnover rate. It is likely that a consequence of a higher rate of turnover is a higher rate of death. The role of the thymus is controversy. While some data point to an important role for the thymus in maintaining T cell numbers and suggest that impairment of thymic function may be responsible for decline in CD4 cell count seen in the setting of HIV infection, other studies have concluded

that the thymus plays a minor role in HIV pathogenesis. Among the data supporting an important role for the thymus are those that demonstrate an increase in the levels of T cell receptor excision circles (TRECs) following initiation of antiretroviral therapy. TRECs are a byproduct of T cell development and represent episomal fragments of DNA that are excised during T cell receptor gene rearrangement. Levels of TRECs will be the net result of changes in thymic output and changes in T cell turnover will lead to an increase in levels of TRECs. While it is clear that levels of TRECs increase following initiation of antiretorival therapy, it is not clear whether this is a consequence of increased thymic output or decreased T cell turnover.

Increases in both CD4 and CD8 cell death and impairment in function are the sine qua non of HIV infection. IL-2 partially corrects the impaired lymphocyte proliferation and cytotoxicity seen in HIV infection in vitro.

It also partially blocks the tendency of lymphocytes obtained from HIV infected patients to undergo apoptosis[41]. In phase I trials of IL-2 in HIV infected patients, it increased CD4 cell number and improved lymphocyte function[41].

The development of a long acting polyethylene glycol modified IL-2 which increases the half life by 10-15 fold allows intermittent administration of the drug.

In 1993, revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults, CD4 cell categorization has been done as,

i) >500/micro litre

ii) 200-499/micro litre

iii) <200/micro litre

CONSEQUENCES OF LYMPHOPENIA:

CD4 T cell count is accepted as best indicator of the immediate state of immunologic competence in patients with HIV infection. Patients with CD4 T cell counts <200/microlitre are at high risk of infection with p.carinii while those with counts <50/ microlitre are at risk of cytomegalo virus and mycobacterium avium (MAC) complex infection. Hence CD4 T cell measurements should be done at the time of diagnosis and every 3-6 months thereafter.

CD4 T cell count <350/ microlitre is an indication of initiating anti retroviral therapy and decline in count >25% from the base line

CD4 count warrant change in therapy. Thrush due to candidal and oral hairy leukoplakia occur in CD4 count < 300/micro litre.

All patients with HIV infection about to undergo splenectomy should be immunized with pneumococcal polysaccharide. It should be noted that, in addition to causing an increase in the platelet count, removal of the spleen will result in an increase in the peripheral blood lymphocyte count, making CD4+ T cell counts unreliable. In this setting, the clinician should rely on the CD4+ T cell percent for making diagnostic decisions with respect to the likelihood of opportunistic infections. A CD4+ T cell percentage of 15 is approximately equivalent to a CD4+ T cell count of 200/μl.

THROMBOCYTOPENIA

Thrombocytopenia is relatively common during the course of HIV infection, occuring in approximately 40% of patients and serving as the first symptom or sign of infection in approximately 10%[42,43]. Development of thrombocytopenia was associated with

i) history of clinical or immunologic AIDS

ii) injection drug abuse

iii) history of anemia or lymphoma

iv) being an American or African descent.

After controlling for multiple factors, thrombocytopenia was significantly associated with shorter survival (risk ratio 1.7)[43]

The incidence of thrombocytopenia, defined as a platelet count less than 150,00/ml, was evaluated among 1990 HIV-infected and 553 HIV-negative women who were part of The Women's interagency HIV Study (WIHS). At baseline, 15 percent of HIV-positive women were thrombocytopenic compared to 1.6 percent of

HIV-negative women ($p<0.001$). Factors associated with increased risk of thrombocytopenia included

(1) HIV infection,

(2) Low CD4 levels

(3) Increasing viral load

(4) Smoking, and

(5) being an American of European descent.

The study also found thrombocytopenia was significant predictor of both all - cause and AIDS-related mortality among women infected with HIV. Thus, HIV-infected women with a platelet count less than 50,000/ml had a fivefold increased risk of death from any cause compared to women with normal platelet courts (hazard ratio [HR] 5.10, 95% CI 2.71-9.58) and an approximately threefold increased risk of death from AIDS (HR 3.36, 95% CI 1.44-7.83).

CAUSES OF HIV-RELATED IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

i) Increased platelet destruction

ii) Decreased platelet production

iii) Infection of Megakarocytes by HIV

iv) HIV related thrombotic thrombocytopenic purpura (TTP)

i) Increased platelet destruction:

As in ITP, HIV infected patients with ITP also demonstrate increased platelet destruction via phagocytosis by Macrophages in the spleen[44]. Presence of platelet specific antibodies characterized as anti group IIb/IIIa have been detected in HIV infected patients[45].

However cross reactive antibody between HIV Gp 160/120 and platelet GP IIb/IIIa may be operative in immune destruction of platelets in HIV related ITP. Absorption of immune complexes against HIV into platelet FC receptor, providing 'free' FC portion for macrophage binding and phagocytosis[45].

ii) Decreased platelet production:

Mean platelet survival was significantly decreased in patients with HIV-ITP occuring to same extent in patients receiving AZT and those untreated. Mean platelet survival also was significantly decreased in HIV infected patients with normal platelet count.

Mean platelet production was significantly decreased in patients with untreated HIV ITP although those receiving AZT demonstrated a subsequent rise in platelet production.

iii) Infection of Megakarocytes by HIV:

Reduced production of platelets may be due to direct infection of megakaryocyte by HIV. Human megakaryocytes bear a CD4+ receptor capable of binding HIV[47] and HIV 1 can be internalized by human Megakacyocytes[48].

The HIV 1 coreceptor CXCR4 is present on Megakayocytic progenitors, Megakaryocytes and platelets. Using in situ hybridization HIV transcripts have been detected in megakaryocytes. Specific ultra structural damage in HIV infected megakaryocytes consisting of blebbing and vacuolization of surface membrane[50].

iv) HIV related thrombotic trrombocytopenic purpura (TTP)

HIV infection is associated with an increased incidence of TTP and hemolytic uremic syndrome characterized by Microangiopathic hemolytic anemia and thrombocytopenia with or without end organ failure. HIV related TTP generally has milder cause and better response to therapy than classical TTP[51].

HIV can infect endothelial cells, and viral P_{24} antigen has been detected in splenic endothelial cells, spinal cord specimens and in bone marrow microvascular endothelial cells[52].

TNF-α and IL-1β are increased in HIV infection could potentially lead to increases in endothelial expression of adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule and E-selectin promoting localization of inflammatory cells to endothelium. Endothelial cells from small blood vessels undergo apoptosis when exposed to plasma from patients with TTP[53].

MATERIALS

SUBJECTS

All patients with HIV infection attending Govt. General Hospital between May 2005 - May 2007.

PERIOD OF STUDY

May 2005 to May 2007.

DESIGN OF STUDY

Prospective Study

ELIGIBILITY CRITERIA

1. All patients with HIV infection
2. HIV infection proven by ELISA & western blot assay.

EXCLUSION CRITERIA

1. Chronic infection like tuberculosis
2. Alcoholics
3. Worm infestations
4. Chronic kidney disease
5. Drug intake (phenytoin)
6. Patient on anti retroviral therapy

METHODOLOGY

All patients with HIV infection attending Govt. General Hospital during the study period were evaluated for the conditions which could alter the Hematological parameters and if found so, they were excluded from the study.

Those included in the study were investigated for Hb% total count, differential count, ESR and platelet count. CD4 count done by flow cytometric analysis was obtained. They were staged as per the WHO clinical staging given by the National AIDS control organisation (NACO)

[65]*Normal Values of parameters Assessed*	*Male*	*Female*
Erythrocyte sedimentation rate	1 to 25 mm/Hr	0 to 17 mm /Hr
Haemoglobin	13.5 to 17.5 g/dl	12.0 to 16.0 g/dl
Total leucocyte count	4.5 to 11.0 x 10^3/mm^3	
Differential count	Neutrophils 40 to 70%	
	Lymphocytes 22 to 44 %	
	Monocytes 4 to 11%	
	Eosinophil 0 to 8%	
	Basophil 0 to 3 %	
CD4 count	<950 cells/microlitre	
Platelet count	1.5 to 3.0 lakh / mm^3	

WHO CLINICAL STAGING (NACO)

- Stage I
  - Asymptomatic
  - Persistent generalised lymphadenopathy
  - Performance scale 1:asymptomatic normal activity.
- Stage II
  - Wt. loss < 10% of body weight
  - Minor muco cutaneous manifestation (seborrheic dermatitis, fungal nail infection, recurrent oral ulcers, angular chelitis)
  - Herpes zoster (within last 5 years)
    Recurrent upper resp. infection (bacterial sinusitis)
    Performance scale 2: Symptomatic, normal activity.
- State 3
  - Wt loss > 10% body weight
    unexplained chronic diarrhea >1 month unexplained fever (intermittent/continuous) > 1 month
  - Oral Thrush
  - Oral hairy leukoplakia
  - Pulmonary TB within past 1 year.

- Severe bacterial infection (preumonia, pyomyositis)
- Performance Scale 3: bed ridden for <50% of day in last 1 month.

- Stage 4
  - HIV wasting synd (>10% BW loss + Unexplained fever (or) Unexplained diarrhoea >1 month chronic weakness)
  - Pneumocystitis carnii pneumonia
  - Toxoplasmosis of brain
  - Cryptosporidiasis with diarrhea >1 month
  - Cyptococcosis (extra pulmonary)
  - Cytomegalo viral disease of organ other than liver, spleen and lymph node
  - Herpes simplex infection, Mucocutaneous >1 month (or) visceral
  - Progressive multifocal leukoencephalopathy
  - Disseminated endemic mycosis, histoplasmosis, Coccidiodomycosis

- Candidiasis of oesophagus, trachea, bronchi lung
- Atypical; Mycobacterial infection
- Non typhoid salmonella septicaemia
- Extra pulmonary tuberculosis
- Lymphoma
- Kaposi sarcoma
- HIV encephalopathy
- Performance scale 4: Bed ridden for >50% of day in last 1 month.

STATISTICAL ANALYSIS

Data entry and analysis done values are presented as Mean± Standard deviation and median ±Q (interquartile range) as appropriate. Percentages were used to describe the proportions of discrete variables. A p value of <0.05 was considered statistically significant.

OBSERVATIONS

100 patients with HIV infection were included in the study after excluding for all possible parameters that could affect the blood cell counts. Before the initiation of anti retroviral therapy they were investigated for Hb, total count, differential count, CD4 count, platelet count and erythrocyte sedimentation rate (ESR). The observations of the study are as noted below:

AGE DISTRIBUTION:

Table No.1

Age (in yrs)	*n*	*%*
21-25	2	2.0
26-30	15	15.0
31-35	29	29.0
36-40	27	27.0
41-45	20	20.0
45-50	5	5.0
51-55	2	2.0

The mean age was found to be 36.85$\pm$6.29.

SEX DISTRIBUTION:

Table No. 2

	n	***%***
Male	60	60%
Female	40%	40%

WHO STAGE DISTRIBUTION:

Table No.:3

Stage	***n***	***%***
I	4	4%
II	29	29%
III	55	55%
IV	12	12%

Majority of them were in Stage III and least of them were in Stage I.

TOTAL COUNT DISTRIBUTION:

Tabole No:4

Total count (cells/mm^3)	***n***	***%***
2000-3000	9	9%
3001-4000	22	22%
4001-5000	11	11%
5001-6000	13	13%
6001-7000	8	8%
7001-8000	14	14%
8001-8000	16	16%
9001-10000	7	7%

The mean total count was found to be 587$\pm$ 2210 cells / mm^2 out of the 100 patients 41 of them had leucopenia.

DIFFERENTIAL COUNT

In our study the differential count distribution showed

- neutropenia in 30 patients
- lymphocytopenia in 30 patients and
- monocytopenia in 20 patients.

Table No. 5

White Blood Cells	***mean***
Neutrophils	54±12.6%
Lymphocytes	29.8±8.3%
Monocytes	6.76±4.1%
Eosinophils	2.36±3.79%
Basophils	0%

CD-4 COUNT DISTRIBUTION

Table No. 6

CD4 Count (Cells/microlitre)	***n***	***%***
<200	87	87.0
200-499	13	13.0
≥ 500	0	0

The median CD-4 count was 89 cells/microlitre.

Almost all the patients enrolled in our study had CD4 count <200/microlitre with only a minor fraction having counts >200/microlitre.

CD 4 COUNT & LYMPHOCYTOPNEIA:

Table No:7

CD4 Count (Cells/microlitre)	*n*	*%*
<200	30	100%
200-499	0	0
≥ 500	0	0

All patients who had lymphocytopenia were having CD4 count <200/microlitre. This establishes the relationship between lymphocytopenia and low CD4 counts.

PLATELET COUNT DISTRIBUTION

Table No : 8

Platelet Count (Lakh/mm^3)	***n***	***%***
<0.5	0	0
0.5 - 0.99	21	21.0
1.00 - 1.49	19	19.0
1.50 - 1.99	37	37.0
2.00 - 2.49	15	15.0
2.50 - 2.99	7	7.0
$\geq$ 3	1	1.0

The mean platelet count was 1.56 $\pm$ 0.35 lakh / mm^3 thrombocytopenia was found in 40 patients.

ERYTHROCYTE SEDIMENTATION RATE

Table : 9

Elevated ESR (mm/hr)	*n*	*%*
Male	41	21.0
Female	30	20.0

The mean value ESR was 24.63 $\pm$ 10.92 mm /hr. Elevated ESR was found in 71%. ESR has not much of diagnostic value and therefore can be elevated in any chronic inflammation (or) infection. Hence, this finding may not be that significant.

HEMOGLOBIN DISTRIBUTION

Table No. 10

Hemoglobin g/dll	*Male*	*Female*	*%*
8.0 - 8.99	1	1	2.0
9.0 - 9.99	10	3	13.0
10.0 - 10.99	12	11	23.0
11.0 - 11.99	16	9	25.0
12.0 - 12.99	16	13	29.0
13.0 - 13.99	8	0	08.0

The mean Hb value was 11.40 $\pm$ 1.36 g/dl.

Table No: 11

Sex	*Anemia*	*%*
Male	55	87.3%
Female	24	64.9%

Male were found to have anemia more commonly than female patients.

WHO STAGE WISE DISTRIBUTION OF HAEMATOLOGICAL ABNORMALITIES

Table : 12

Abnormalities	***I***	***II***	***III***	***IV***	***P***
Leucopenia	2	12	21	6	0.87
Neutropenia	2	9	16	2	0.62
Lymphocytopenia	-	9	18	3	0.56
Moncytopenia	-	5	12	4	0.49
Thrombocytopenia	2	12	20	6	0.57

The WHO clinical stage wise analysis of the Hematologic abnormalities were not found to be statistically significant. Hence any possible association between WHO stage and cytopenias could not be found.

WHO STAGING & ANEMIA

Table : 13

Anemia	*I*	*II*	*III*	*IV*	*P*
Male	-	12	35	8	0.04
Female	0	10	13	1	0.005

The WHO clinical stages and anemia correlation was found to be statistically significant. Hence a possible relationship found between anemia & WHO stages.

DISCUSSION

The observation made in the PLHAs with respect to Hemoglobin total count differential count, platelet count, CD4 count, erytrocyte sedimentation rate and WHO stages were analysed and the following inferences were drawn.

AGE DISTRIBUTION

The mean age of the study population was 36.85± 6.29 yr. About 56% of them were in 31-40 year age group i.e., age at the diagnosis of HIV infection.

As per the data released by Tamil Nadu State AIDS control society (TANSAC) about 50% of HIV infected patients belonged to 30 - 49 years at the time of diagnosis [(54)].

In the western countries about 36% of them were in the 35-44 years age group at the time of diagnosis, which happens to be the Major age group affected [(55)].

Our data is in concordance with these data.

SEX DISTRIBUTION

In our study population 60% were males and 40% females. The M:F ratio was 3:2. The sex ratio of PLHA is at the time of diagnosis was 8:3 in India[54] and 7:3 in western countries[55].

The ratio was altered in our study probably, because more males got excluded who were alcoholics. Hence our sex ratio differed from those of the surveillance reports.

WHO STAGE DISTRIBUTION

Majority of the PLHA's (about 55%) belonged to stage III at the time of diagnosis whereas only 4% were in stage I. Hence the diagnosis of HIV infection was considerably less in the asymptomatic stage and most of them were diagnosed only with features of full blown AIDS and Opportunistic infections.

This implies the fact that, most of the PLHA's at diagnosis had full blown AIDS and hence would develop most of the complications and opportunistic infections. Initiation of retroviral therapy would only add on to the morbidity.

TOTAL COUNT ABNORMALITIES

The mean total count in our study was 5872 ±2210 cells / mm^3. The total count varied between 2000 to 10,200 cells/mm^3. 41% of them had leucopenia.

The percentage of PLHA's with leucopenia at the time of diagnosis was found to 16% and 25% by Amballi et al [56] and Amanda[57] et al respectively. Erhabor et al, in his study on the effect of anti retroviral therapy an hemotological profile of people PLHA's found leucopenia in 62%[58].

Higher incidence of leucopenia in our study may be due to the diagnosis of HIV infection at advanced stage. This again reiterates the fact that diagnosis of HIV infection at advanced stage would increase the incidence of complication.

The awareness campaigns and counselling programs has to be intensified, so that the diagnosis of HIV infection can be done at earlier asymptomatic stage.

NEUTROPENIA

The mean neutrophil count was 54 ± 12.6% and in our study 21% had neutropenia. Where as Amballi et al found 42.4% of PLHA's to have neutropenia at the time of diagnosis of HIV infection[56].

In our study, out of the 21 persons who had neutropenia, 18 were in advanced stage of HIV disease (stage III & IV) and 2 were in early asymptomatic stage of HIV infection (Stage I). Zon and groopman noted neutropenia in 13% of asymptomatic HIV infected patients and in 44% of those with frank CDC - defined AIDS [4].

In the multistate adult and adolescent spectrum of HIV disease surveillance project neutropenia was detected in10% and 50% of asymptomatic patients and advanced stage of HIV disease patients respectively[5]. Hence the occurence of neutropenia was lesser in our study.

In our study more patients in advanced stage of HIV infection were having neutropenia. This poses them at the increased risk of developing opportunistic infections.

LYMPHOCYTOPENIA & CD4 COUNT

The mean lymphocyte count was 29.82 ± 8.3% and the median CD4 count was 89 cells/micro litre. CD4 count varied between 6 cells to 459 cells/ml Lymphocytopenia was found in 30% of the PLHA's and CD4 count <200 cells in 87% of the patients.

In the study conducted by Amballi et al the median CD4 count was 160 cells. They detected lymphopenia and CD4 count <200/microlitre in 24.3% and 62.8% respectively[56].

In our study majority of the PLHA's (67%) were in advanced stage (III & IV) of HIV infection and hence higher incidence of lymphocytopenia and CD4 <200/microlitre.

The findings of low CD4 count in 87% of patients and lymphocytopenia in 30% is in accordance with WHO document an clinical staging of HIV / AIDS for adults and adolescents, which ascertained both lymphopenia and CD4 cells depletion in HIV / AIDS[59]

THROMBOCYTOPENIA

Platelet count varied between 0.5 to 2.8 lakh/mm3 and the mean count was 1.56 $\pm$ 0.35 lakh/$mm^{3.}$ Thrombocytopenia was founds in 40% of the PLHA's is our study. In his study conducted among HIV positive pregnant women khandekar et al, found thrombocytopenia in 9% of them[(60)].

Pechere et al detected thrombocytopenai in 40% of HIV infected patients during the course of the disease and as the first symptoms or sign of HIV infection in approximately 10%[(42)].

Murphy et al concluded that thrombocytopenia was found in 30% (6 of 20) of patients with advanced HIV disease and 8% (5 of 59) in those with asymptomatic HIV infection[(61).] In our study it was found in 38% (26 of 67) and 42% (14 of 33) of advanced HIV disease and asymptomatic HIV infection respectively.

Savona et al concluded that in HIV infection, early stages may have decreased platelet count due to decreased survival and in late advanced disease due to marrow failure[(62)].

ANEMIA

The mean Hemoglobin in our study was 11.4 ±1.36 g/dl and it varied between 9g/dl to 14g/dl. In our study 79 patients had anemia out of which 55 (87.3%) were males and 24 (64.9%) were females. The occurrence of anemia was found to be more common among males.

Amballi et al found anemia in 52% of PLHA's [56]. Anemia was reported as a consistent hematological abnormality in HIV/AIDs by Ogun et al [63]. Mitsuyasu et al and Zon et al detected anemia in approximately 10 to 20% at initial presentation and in 70 to 80% over the course of HIV infection (3,4).

Anemia is an independent predictor of survival in HIV infection and mortality is increased by 60% in anemia patients with CD4 <200/ microlitre[26]. In our study 79% had anemia and 87% had CD4 <200/ml. This high lights the possibility of increased mortality in our set of patients. The institution of HAART in these patients has the chance of converting them into transfusion dependent anemia patients.

ERYTHROCYTE SEDIMENTATION RATE

The mean ESR was 24.63 ± 10.92 mm/hr and varied between 10 to 50 mm/hr. Elevated ESR was found in 41% of the PLHA's Amballi et al found elevated ESR in 95% of his patients with HIV infection[56].

The prominent elevation of ESR in all these patients is not surprising. Although ESR is neither sensitive not specific when used as a general screening test, it is usually elevated in the presence of infectious disease and chronic illness[64].

WHO STAGES & HEMATOLOGIC ABNORMALITIES

The analysis of the association between WHO staging of AIDS and thrombocytopenia, neutropenia, lymphocytopenia, leucopenia were not statistically significant.

In contrast the correlation between anemia and WHO staging was statistically significant. The occurrence of anemia was 75% (22 of 29) in stage II, 87% (48 of 55) in stage III and 75% (9 of 12) in stage IV. As such occurrence of anemia was higher in all stages, slightly higher in stage III.

Sulliram et al in the multistate Adult and adolescent spectrum of HIV disease surveillance project reported that the incidence of anemia increased with clinical stages of disease in HIV infection. They found anemia in 3%, 12% and 27% among those with HIV infection alone, immunologic AIDS (CD4<200/ml or CD4% <14%) and clinical AIDS respectively[5].

CONCLUSION

- 100 PLHA's were analysed for the Hematological abnormalities in HIV/AIDs.
- Majority of them were in stage III (55%) and had CD4 count <200/microlitre (87%).
- Leucopenia was found in 41% of them.
- Neutropenia was detected in 29%.
- Thrombocytopenia was found in 40%
- Anemia and elevated ESR detected in 79% and 71% respectively.
- Lymphocytopenia was detected in 30% of PLHA's who also had low CD 4 count as per the WHO documents.
- The analysis of correlation between WHO staging and hematologic abnormalities revealed statistically significant relation only with anemia.

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MASTER CHART

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
1.	Vijaya	34	F	III	8400	64	32	4	0	0	0.75	38	11.2	11
2.	Ravikumar	34	M	III	3400	50	45	5	0	0	0.58	58	10.2	25
3.	Ponnurangam	44	M	III	9400	66	32	2	0	0	1.6	26	12.4	30
4.	Ramaswamy	38	M	IV	6600	70	30	0	0	0	1.5	55	11.2	36
5.	Dhanalakshmi	32	F	III	3000	35	15	10	0	0	1.55	17	14.0	35
6.	Mani	36	M	II	4100	39	19	15	5	0	1.65	86	13.5	18
7.	Jona	34	M	III	4200	38	20	10	4	0	2.0	171	14.0	25
8.	Shanmugam	35	M	III	3900	40	20	10	10	0	1.8	79	13.0	15
9.	Pencil Nagaiah	29	M	III	3200	36	21	10	10	0	1.9	53	14.0	20
10.	Narayanan	40	M	II	8600	61	32	7	0	0	2.1	23	12	35
11.	Dhanabalan	36	M	II	8600	61	33	6	0	0	2.7	18	12	15
12.	Sagayaraj	37	M	II	4000	60	35	5	0	0	1.6	179	11.8	20
13.	Sugumaran	41	M	IV	3900	70	28	2	0	0	0.8	123	12.0	26
14.	Venkatesan	34	M	IV	2600	55	25	10	5	0	0.65	11	13.0	20
15.	Shanthi	28	F	III	8100	63	35	2	0	0	1.7	9	10	45

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
16.	Balasubramanian	41	M	III	7200	66	33	1	0	0	1.8	15	11	30
17.	Manickam	32	M	IV	8900	63	32	5	0	0	1.9	9	12	35
18.	Vasantha Kumari	26	F	IV	5200	48	52	0	0	0	1.7	117	12	40
19.	Geetha	32	F	III	6000	70	31	3	0	0	1.8	59	11	50
20.	Babu	38	M	III	8900	66	31	5	0	0	1.75	153	11.5	45
21.	Gunasekar	34	M	III	6000	65	30	5	0	0	1.6	191	12.0	30
22.	Annamalai	30	M	II	7100	70	29	1	0	0	1.6	159	11.2	35
23.	Masthan	50	M	III	8100	64	32	4	0	0	2.1	102	10.6	35
24.	Kavitha	42	F	I	7100	60	35	5	0	0	2.0	184	12.2	30
25.	Barathy	21	F	III	7400	63	32	5	0	0	0.60	6	10.2	35
26.	Subramani	37	M	III	9400	55	40	5	0	0	0.70	77	12.5	18
27.	Sivaraman	40	M	III	3300	35	20	15	5	0	2.5	160	12.0	10
28.	Thirunavukarasu	2.8	M	II	4000	38	21	16	6	0	2.8	103	11.0	12
29.	Lakshmi	34	F	II	7800	61	35	4	0	0	1.6	125	10.2	30
30.	Vimala	41	F	III	3000	39	20	20	10	0	2.5	57	12.0	15
31.	Nathan	48	M	III	3100	36	21	20	9	0	2.7	132	13.0	16

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
32.	Dhanasekar	36	M	III	8600	58	37	5	0	0	0.55	37	11	30
33.	Devakumar	32	M	III	7900	76	21	3	0	0	0.65	194	10.2	5
34.	Geetha	38	F	I	2600	38	25	10	15	0	2.8	205	14.0	10
35.	Chinna Thai	27	F	III	8600	64	32	4	0	0	2.7	195	11.2	36
36.	Latha	30	F	I	3900	35	22	10	10	0	1.8	177	12.0	10
37.	Kishna Moorthy	30	M	II	4000	39	21	10	10	0	0.80	44	13.5	10
38.	Mangilal	40	M	III	4100	60	20	15	5	0	1.9	22	14.0	10
39.	Antony Samay	35	M	II	3800	63	21	15	2	0	0.70	32	13.6	10
40.	Selvam	42	M	II	3600	39	25	10	10	0	1.85	133	12.0	15
41.	Chellammal	29	F	II	3400	35	15	10	10	0	1.1	123	13.0	19
42.	Subashree	37	F	I	7800	61	34	5	0	0	1.2	191	13.2	25
43.	Kuppu	35	F	II	7600	52	40	8	0	0	1.95	19	11.9	20
44.	Gurunathan	38	M	III	3000	39	21	10	10	0	1.75	28	12.0	25
45.	Selvakumar	38	M	III	2000	38	21	9	8	0	1.65	87	11.0	26
46.	Arumugam	40	M	IV	2100	37	21	11	9	0	0.75	121	10.0	30
47.	Muthu	41	M	III	8400	58	38	4	0	0	1.70	459	10	36

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
48.	Varadharaju	45	M	IV	2600	35	20	11	6	0	0.65	17	10	25
49.	Shanmugakani	32	F	II	3500	38	21	10	7	0	1.80	205	11.0	28
50.	Sekar	44	M	III	8600	67	28	5	0	0	0.65	30	10.6	16
51.	Durairaj	38	M	III	3700	36	20	11	8	0	1.4	59	10.0	15
52.	Mariamma	33	F	III	3800	39	21	10	7	0	1.95	99	11.0	16
53.	Baby	40	F	III	4400	37	20	9	7	0	1.0	38	9	20
54.	Sairam	47	M	III	7000	70	26	4	0	0	1.90	57	9	25
55.	Elumalai	40	M	III	4300	38	20	10	6	0	0.95	43	10	20
56.	Musthapa	43	M	III	4100	37	21	9	8	0	1.70	81	10	25
57.	Syed Ahmed	42	M	II	4000	39	20	8	8	0	1.1	71	11.0	28
58.	Kuppusamy	38	M	III	3900	35	20	10	9	0	1.75	190	11.2	30
59.	Paneer Selvam	50	M	III	7600	64	33	3	0	0	1.65	199	10.3	65
60.	Nazeema	30	F	IV	8200	59	37	4	0	0	1.70	95	9	15
61.	Partha Sarathy	42	M	IV	5800	66	25	9	0	0	1.2	52	10.6	10
62.	Elangovan	38	M	III	4000	38	21	10	8	0	1.55	34	10.0	30
63.	Sara	33	F	II	3900	39	21	11	7	0	1.60	356	10.5	35

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
64.	Sivanandhan	42	M	III	3600	60	36	4	0	0	1.0	121	12	12
65.	Irrison	52	M	II	5800	45	46	9	0	0	2.1	41	10	14
66.	Babu	35	M	II	6600	60	35	5	0	0	2.1	186	13.1	12
67.	Elumalai	39	M	II	4100	38	21	10	7	0	1.0	50	10.0	10
68.	Kuppan	35	M	III	7800	53	44	3	0	0	1.2	61	12	20
69.	Vijaya	28	F	IV	2400	60	34	6	0	0	2.4	11	12	25
70.	Govindaraj	45	M	II	5800	68	30	2	0	0	0.80	202	10.8	10
71.	Lakshmi Kanthamma	38	F	II	7200	54	40	6	0	0		15	10.6	11
72.	Malliga	31	F	III	9400	63	34	3	0	0	2.3	39	12.5	16
73.	Abdhul Razak	33	M	III	9200	60	33	7	0	0	1.2	340	11.6	17
74.	Tamil Selvi	28	F	III	6900	58	37	8	0	0	1.3	79	12.0	25
75.	Selvaraj	40	M	III	4200	49	38	5	0	0	2.5	209	11	19
76.	Ramaswamy	54	M	III	5200	68	30	2	0	0	1.1	29	12	30
77.	Srinivasan	40	M	III	8000	60	37	3	0	0	0.65	173	12.6	30
78.	Gopal	32	M	II	5800	68	30	2	0	0	2.0	134	14.0	35

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
79.	Egambaram	32	M	II	7600	69	29	2	0	0	2.4	386	13.5	40
80.	Sarasu	41	F	III	5100	28	35	7	0	0	2.0	79	10.8	25
81.	Shanmugam	45	M	III	8200	64	34	2	0	0	1.1	206	10.6	20
82.	Paul	35	M	II	8800	68	28	7	0	0	3.0	91	9.7	15
83.	V. Kumar	48	M	III	5300	68	38	7	0	0	1.2	302	10.6	40
84.	Kuppammal	27	F	II	6800	56	40	7	0	0	2.1	70	10	35
85.	Krishnammal	35	F	II	7200	56	40	7	0	0	1.4	200	10.2	36
86.	Uma	30	F	II	9600	60	35	5	0	0	1.1	113	11.0	35
87.	Hema	45	F	III	6000	60	33	7	0	0	2.0	9	10.2	40
88.	Dilli	35	F	II	7000	59	27	4	0	0	1.0	72	8.0	35
89.	Soundarya	24	F	III	6900	60	32	8	0	0	0.70	157	10.2	38
90.	Soundarammal	45	F	IV	4800	46	50	4	0	0	0.75	81	13.4	16
91.	Samundeeswari	38	F	III	9200	64	28	8	0	0	0.80	69	11.8	50
92.	Sridhar	34	M	III	3900	63	28	9	0	0	2.6	49	8.3	15
93.	Kamala	45	F	III	10200	70	25	5	0	0	1.6	180	11.8	20
94.	Sundar	35	M	III	5400	70	24	6	0	0	1.7	145	11.8	25

Sl. No.	Name	Age	Sex	WHO Stage	Total count (per $mm^{3)}$	Differential Count					Platelet Count (lakh/mm^3)	CD4 Count (per µl)	Hb (g/dl)	ESR at 1 hr
						P%	L%	M%	E%	B%				
95.	Venkatesan	36	M	IV	4200	80	19	1	0	0	1.4	138	10.6	26
96.	Manjula	32	F	III	5800	45	46	9	0	0	1.3	140	10.0	19
97.	Kumar	43	M	III	6500	51	44	5	0	0	1.2	197	13	20
98.	Gokila	34	F	II	4300	55	43	2	0	0	1.8	147	9.6	25
99.	Alamelu	30	F	II	8800	59	37	4	0	0	1.9	217	12	20
100.	Ramesh	28	M	III	8400	49	41	10	0	0	1.0	211	12.6	20

PROFORMA

Name : Age : Sex :

Place : Occupation :

Hospital No.

PRESENTING COMPLAINTS :

PAST HISTORY :

H/o. Tuberculosis

H/o. Exposure to a case of tuberculosis

H/o. Drug intake

H/o. Worm passage in stools

H/o. Blood Transfusion

PERSONAL HISTORY

H/o. Alcohol intake

H/o. Smoking

H/o. IV Drug abuse

H/o. Pre marital (or) extra marital exposure

GENERAL PHYSICAL EXAMINATION

Built & Nourishment :

Pallor : Icterus : Clubbing :

Pedal Edema : Lymph Nodes :

Oral Candidiasis :

Herpes Zoster :

Glossitis :

VITAL SIGNS :

Pulse :

Blood Pressure :

Temperature :

Respiratory Rate :

CVS :

RS :

Abdomen :

CNS :

INVESTIGATIONS

Hemoglobin :	Blood Sugar :
Total Count :	Urea:
Differential Count :	Creatinine
CD4 Count :	Electrolytes
Platelet Count :	LFT :
ESR :	
Stool Examination :	
Urine Routine :	
Chest Xray :	
Sputum Examination :	
ELISA :	

Special Investigation :

Final Diagnosis :